CME review article

Supported by a grant from AstraZeneca LP

Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review

Joy L. Snyder, MD* and Guha Krishnaswamy, MD†‡

Objective: Autoimmune progesterone dermatitis is a rare cyclic premenstrual reaction to progesterone produced during the luteal phase of a woman's menstrual cycle with a variety of presentations including erythema multiforme, eczema, urticaria, angioedema, and progesterone-induced anaphylaxis. We present a case of progesterone-induced anaphylaxis and a review of literature focusing on its diagnosis and therapy.

Data Sources: We surveyed all the literature in English back to 1921 when the first case was published. First, we researched the terms progesterone anaphylaxis, autoimmune progesterone dermatitis, cyclic urticaria, using the PubMed resource. Then we included articles found within these publications' reference sections.

Study Selection: We selected articles based on whether the cases described appeared to fit the description of the entity autoimmune progesterone dermatitis. All cases included had dermatologic reactions occurring during the luteal phase of the menstrual period, positive skin or intramuscular reactions to progesterone, and treatment amenable to anovulatory agents and/or hysterectomy with bilateral salpingo-oophorectomy.

Results: We found approximately 50 published cases of autoimmune progesterone dermatitis, and only nine known cases of its manifestation as anaphylaxis. These cases, including the case described by us, are summarized, and successful diagnostic and therapeutic approaches in the literature are reviewed.

Conclusions: Autoimmune progesterone dermatitis is a rare entity associated with progesterone production of the luteal phase of a woman's menstrual cycle. It can be diagnosed using intradermal or intramuscular progesterone tests and can be treated by disrupting the ovulation cycle using specific medications or by oopherectomy.

Ann Allergy Asthma Immunol. 2003;90:469–477.

INTRODUCTION

It is well documented that the menstrual cycle influences systemic diseases such as asthma, acne, porphyria, hereditary angioedema, aphthous ulcers, Behçet syndrome, epilepsy, migraines, myasthenia gravis,[1] and allergic rhinitis.[2] It is, however, not well known that the menstrual cycle may induce a spectrum of cyclic dermatologic conditions referred to as autoimmune progesterone dermatitis (APD) with differing presentations (Table 1) including eczema,[3–7] erythema multiforme (with and without mucosal involvement),[5,8–17] fixed drug eruptions,[16] folliculitis,[18] stomatitis,[10,14,16,17,19] vesiculobullous eruptions,[9,12,20] and urticaria with or without angioedema.[3,9,10,13,15,21–35] Some reported cases progressed later to cyclic anaphylactic reactions, referred to herein as progesterone-induced anaphylaxis.[21,36–38]

The first documented case of cyclic urticaria associated with menses was described by Geber[39] in 1921. He demonstrated a likely hormonal allergy as he challenged a patient with her own premenstrual serum causing a flare in the disease.[39] The same investigator later used desensitization with systematic injections of the premenstrual serum to successfully relieve symptoms.[40] Zondek and Bromberg[41] in 1945 showed a positive Prausnitz-Küstner test or passive transfer test using sera from patients with hormone sensitivity. This process involves taking sera from known estrone-sensitive women and injecting it into normal women. When positive it causes a local skin reaction, indicating that the serum probably contained specific antibodies.[41] Although progesterone sensitivity has been the most well studied of causes, estrogens,[2,8,41–45] gonadotropins,[46] and, most recently, prostacyclins[47,48] have also been cited as possible etiologies for these cyclic allergic reactions.

APD is a rare sensitivity to the high levels of progesterone found in the luteal phase of a woman's menstrual cycle.[49]

* Internal Medicine, Memphis, Tennessee.
† Allergy and Immunology, James H. Quillen V.A. Medical Center, Johnson City, Tennessee.
‡ Department of Medicine, East Tennessee State University, Johnson City, Tennessee.
Received for publication January 14, 2002.
Accepted for publication in revised form October 27, 2002.

Table 1. Autoimmune Progesterone Dermatitis and its Various Manifestations

Anaphylactoid reactions	Dermatologic/mucosal reactions
Premenstrual	Stomatitis
Catamenial	Eczema
	Erythema multiforme
	Stephens-Johnson syndrome
	Fixed drug eruptions
	Folliculitis
	Vesiculobullous reactions
	Urticaria
	Urticaria and angioedema

There are approximately 50 APD cases in English literature, but only nine cases of progesterone-induced anaphylaxis[9,21,36–38,50] and two well documented cases of catamenial anaphylaxis[47,48] (Table 2). Catamenial anaphylaxis differs from APD primarily by the timing of symptoms, which appear to be directly associated with the start of the menstrual flow instead of beginning 3 to 10 days earlier in the premenstrual phase as in APD. In APD, the symptoms end 1 to 2 days into the menstrual flow, but catamenial anaphylaxis continues until the end of menses. It should be noted, in some cases of APD, symptoms persist throughout the entire menstrual cycle or occur at apparently random times of the cycle. Positive skin tests to progesterone or its derivatives, reproduction of symptoms with intramuscular hormonal challenges, and detection of purified antibodies to progesterone or its derivatives have suggested an autoimmune basis for the syndrome.

In this paper, we report on a young woman who had monthly urticarial reactions associated with her menstrual period. These reactions frequently progressed to angioedema and anaphylaxis, and ultimately fit the profile of anaphylaxis attributable to APD. We also review the literature for reported cases of progesterone sensitivity and summarize the findings (Table 2).

CASE REPORT

A 22-year-old female (Gravida 1 Para 1) was referred because of a 2-year history of recurrent monthly urticarial eruptions. The symptoms usually began approximately 3 days before her menstrual period and lasted 5 to 7 days before resolution. The eruption started as itching and swelling with raised plaques usually involving her head and neck. Sometimes flushing occurred around her ears, and at other times it progressed to involve her entire body. On one occasion, it was associated with respiratory distress and was treated with epinephrine in the emergency department. Another time, a few months before evaluation, she had been hospitalized with a syndrome of fever, cutaneous eruption, facial edema, pleural effusions, ascites, and periportal extravasation of fluid. The latter findings were confirmed by computerized tomography and suggested severe anaphylactic sensitivity with a capillary leak-like phenomenon. After careful multispecialty evaluation, the patient was discharged when she improved greatly on a tapering course of prednisone, diphenhydramine (Benadryl, Warner Lambert, Morris Plains, NJ), and cimetidine (Tagamet, SmithKline Beecham, Philadelphia, PA). However, when the steroids were tapered, the syndrome flared on a recurrent basis. The patient was noticed to be taking Ortho Tri-Cyclen (Ortho-McNeal Pharmaceutical, Raritan, NJ) at the time the reactions were occurring. These oral contraceptives contained norgestimate and ethinyl estradiol. The patient was told not to take oral contraceptives and an evaluation was initiated.

She had normal levels for liver and thyroid function tests, and negative radioallergosorbent test for foods and latex (Table 3). Urinalysis was negative for hematuria and proteinuria. Because the differential diagnosis in this case included disorders such as systemic mastocytosis, hereditary angioedema, carcinoid syndrome, parasitic infections, and hypereosinophilic syndrome (Table 4), multiple tests were performed to exclude these diagnoses. These tests and their results are summarized in Table 3.

Because she continued to have flares of mild angioedema always associated with her premenstrual period, she was challenged with medroxyprogesterone (Depo-Provera [DP], Pharmacia and Upjohn, Kalamazoo, MI), conjugated estrogens (Premarin Wyeth-Ayerst, Philadelphia, PA), and diethylstilbestrol. The vital signs on admission were normal. The patient had negative percutaneous tests to conjugated estrogens and diethylstilbestrol. However, when incremental challenge testing was carried out with medroxyprogesterone, reactions occurred. Within 15 minutes after the lowest dose of medroxyprogesterone, the patient began to experience the sensation of flushing, chest tightness, and laryngeal symptoms. Erythema and angioedema of the upper arms and chest with urticaria rapidly developed. She also developed a large nodule on the scalp, which rapidly increased in size. This positive challenge confirmed the diagnosis of progesterone-induced anaphylaxis. The test was aborted, and the patient was hospitalized and treated appropriately for systemic anaphylaxis.

On discharge from the hospital, the patient was treated with H_1- and H_2-blockers. She received frequent symptomatic use of steroid tapers and experienced little long-term remission in her symptoms. She was therefore placed on a therapeutic trial of a luteinizing hormone-releasing hormone (LH-RH) agonist (Lupron, TAP Pharmaceuticals, Deerfield, IL) These were daily injections started at 0.5 mg for 2 weeks and increased to 1 mg daily which led to remission of symptoms. Depo-Lupron 3.75 mg or 7.5 mg monthly or 11.25 mg per 3-month injections were initiated 2 weeks later (physician administration required) to replace the daily injections so therapy might be more convenient for the patient. However, side effects of hot flashes and dizziness and the lifelong nature of the treatment were uncomfortable for the patient. As a more definitive therapy, 9 months later, the patient underwent hysterectomy with bilateral salpingo-oophorectomy with resolution of symptoms.

Table 2. Published Cases of Hypersensitivity Reactions Associated with the Menstrual Cycle

Age (yrs)	Reaction	Duration	Relation to menstruation	Parity	Challenge study	Successful therapy	Reference
AID with anaphylaxis*							
48	Chronic urticaria, angioedema, laryngeal spasm	1 yr	10 days before flow, now constant	N/A	Progesterone positive in 10 minutes and at 48 hours	Desensitization with conjugated estrogens	[9]
36	Urticaria, hypotension, laryngeal edema, bronchospasm	2 yrs of urticaria	Every 5 to 10 days	G7P3Ab4	Positive LH-RH challenge negative challenge with FSH, LH, estrogen, and diethylstilbestrol	LH-RH agonists	[21]
24	Flushing, syncope	2 yrs	Continuous, with premenstrual worsening	G0P0	Medroxyprogesterone caused a flare with no wheal LH-RH agonist—no reaction	N/A	[38] (case 1)
37	Flushing, bloating, laryngeal edema, urticaria	6 yrs	N/A	G1P0Ab1	Medroxyprogesterone caused a systemic reaction. LH-RH agonist positive in 30 to 60 minutes	LH-RH agonists, TAH-BSO†	[38] (case 2)
30	Flushing, laryngeal edema, nausea, urticaria	8 yrs	N/A	G0P0	Medroxyprogesterone—no reaction	N/A	[38] (case 3)
42	Flushing, facial edema, urticaria, syncope, and genital hives	15 yrs	N/A	G2P2; previous dysfunctional uterine bleeding	Medroxyprogesterone caused a wheal whereas LH-RH agonist caused a systemic reaction	LH-RH agonists, TAH-BSO	[38] (case 4)
22	Flushing, facial edema, urticaria, pleuritis, ascites	2 yrs	3 days before menses lasted 5 to 7 days	G1P1; previous oral contraceptive	Depo Provera caused a systemic reaction within 15 minutes of lowest dose	LH-RH agonists TAH-BSO	Our patient
Catamenial anaphylaxis							
40	Urticaria, angioedema, shock, laryngeal edema	2 yrs	At start of menstrual flow	N/A	Menstrual fluid caused a positive reaction‡	N/A	[47]
35	Stridor, laryngeal edema, urticaria, hypotension	9 months; 2 previous urticarial episodes	At start of menstrual flow	Used oral contraceptives which caused a DVT	Medroxyprogesterone caused a slight reaction; negative to progesterone and conjugated estrogens	Indomethacin for 1 month then TAH-BSO	[48]
Depo-Provera reactions							
22	Urticaria, facial edema, hypotension	Postpartum	N/A	G3P2	Postpartum Depo Provera injection caused a reaction within 3 minutes	N/A	[36]
46	Urticaria, hypotension	N/A	N/A	Previous norethisteronean	Depo Provera caused an immediate reaction	N/A	[50]

Abbreviations: AID, autoimmune dermatitis; DVT, deep vein thrombosis; FSH, follicular stimulating hormone; IM, intramuscular; LH, leuteinizing hormone; LH-RH, luteinizing hormone-releasing hormone; N/A, not applicable; TAH BSO, total abdominal hysterectomy and bilateral salpingectomy; yrs, years.

Notes:

*3 patients have been noted with idiopathic anaphylaxis, all having negative skin tests to progesterone, but positive intramuscular challenges to progesterone were recorded.

†This patient's symptoms decreased from 17–35 episodes a week to 4–7 per week, but did not fully remit. She still requires H_1- and H_2-receptor antagonists for control.

‡Positive immediate reaction which disappeared in 90 minutes, and later showed 2-mm induration at 24 hours. Negative testing to pregnanediol, allopregnanediol, estrone, estradiol, estriol.

The table is divided into three categories of patients, the progesterone sensitive patients, the catamenial anaphylaxis patients, and patients with solitary reactions to Depo Provera. The progesterone sensitive patients showed symptoms beginning in the premenstrual time period a few days prior to flow, and the catamenial anaphylaxis patients delayed their symptoms until the initiation of menstrual flow. It should be noted that the symptoms of patients 1, 2 and 3 had become continuous or at least occurred throughout the month without regard to the menstrual cycle. Most patients had some sort of reaction to administration of progesterone or LH-RH agonists.

Table 3. Laboratory Results, Case Presentation

Abnormal labs
IgE to 841 IU/mL (elevated)
Normal labs
Liver function tests
Thyroid function tests
Urinalysis was negative for hematuria and proteinuria
RAST for foods and latex
ANA, RF, ESR
C3, C4, IgG, IgM, IgA
Serum tryptase
24-Hour urine for histamine
Urine 5-H1AA
C1 esterase functional antigen
Strongyloides IgG
Stool O&P

RAST, radioallergosorbent test; ANA, antinuclear antibody; RF, rheumatoid factor; ESR, erthrocyte sedimentation rate; O&P, ova and parasites exam.

Table 4. Differential Diagnosis of Recurrent Anaphylactic Symptoms

Systemic anaphylaxis attributable to known etiologies
Food, drug, latex, venom, infections, lupus
Systemic mastocytosis
Hereditary angioedema
Carcinoid syndrome
Parasitic infections
Hypereosinophilic syndrome
Other syndromes
Exercise-induced anaphylaxis
Food-dependent/independent
Systemic urticaria
Cold/cholinergic
Autoimmune progesterone dermatitis
Dermatologic manifestations
Anaphylactoid manifestations
Catamenial anaphylaxis
Idiopathic anaphylaxis (diagnosis of exclusion)

APD AND ANAPHYLAXIS

This patient demonstrated all the classical manifestations suggesting sensitization to the hormone progesterone. This resulted in cutaneous manifestations but ultimately led to the more serious evolution into systemic anaphylaxis. The following sections discuss the pathogenesis, manifestations, and clinical management of the disorder.

Pathogenesis

It is probable that there are several mechanisms at work in the disease process of APD, as there is a multiplicity of manifestations and differences in test results in the various studies in literature. In particular, the variety of types of reactions on intradermal/intramuscular testing seems to indicate some differences in causes. For instance, some reactions are immediate, occurring within minutes of testing. Others are delayed, with symptoms taking hours to appear; and still others have both kinds of reactions. Alternatively, there could be several different possible defects in the mechanism involving progesterone causing the variation of manifestations. Some possibilities include stimulation of type 2 T helper cells by progesterone (which in turn regulate immunoglobulin [Ig]E synthesis and allergic disease), direct effects of progesterone on mast cells and basophils versus progesterone serving as an autoantigen and inducing antibody responses. These antibodies reacting with the hormone can induce immune reactions in susceptible individuals. These mechanisms are summarized in Figure 1.

Sensitized by What?

Because the sensitivity involved endogenous and exogenous hormones, Meltzer[44] pointed out that sensitization could occur through previous use of exogenous progesterone. An interesting thought, however, as some women have never been exposed to exogenous progesterone,[17,25,28,35,51] this hypothesis may be true in some but not all cases. An alternative mechanism for sensitization might be steroid cross-sensitivity. Schoenmakers et al[7] demonstrated cross-sensitivity between hydrocortisones and 17-α-hydroxyprogesterone (17-OHP) through patch testing in 5 of 19 corticosteroid-sensitive women. Only two women actually had symptoms of APD. Although the hypothesis[33] itself still seems feasible, patch testing proved to be unreliable for APD patients when, in a separate study, no other patients who patch tested positive for both steroids had APD symptoms.

Another possible theory could be that a patient might tolerate low levels of her own hormones, but as endogenous levels of progesterone rise during the menstrual cycle or pregnancy, a critical level of progesterone may be reached at which the woman's body reacts to her own progesterone.[44] There have been cases where women became sensitized at the onset of menarche[13,15,52] and at only 1 year after menarche,[14] although the majority of cases become symptomatic later in life. Similarly, during pregnancy, the progesterone levels rise as a result of additional placental progesterone production.[46,53]

Several different patterns of symptomatology occur in pregnancy. The onset of the progesterone sensitive rash can manifest during pregnancy with or without later premenstrual recurrences.[13,17,18,27] First-time symptoms may occur during the postpartum period[20,25,34,41,53] as the menstrual cycle undergoes regularization. Still others have symptoms starting during cycles before pregnancy and are worsened by pregnancy,[5,13,14,17,18,21,35] four of whom have been associated with either spontaneous abortions[5,18] or a history of spontaneous abortions.[13,21] This pattern suggests an accompanying alteration in the patient's immune response for some women.[26] Pregnancy itself may sensitize the patient to progesterone or one of its metabolites, as pregnancy itself alters the immune response. Georgouras[26] postulated that in some specific cases of APD exacerbated by pregnancy (as well as other dermatoses of pregnancy such as prurigo herpes gestationis), the disease may indicate a breakdown of immune tolerance that characterizes a normal pregnancy. There have also been other cases[10,14,35] where the disease worsened during pregnancy

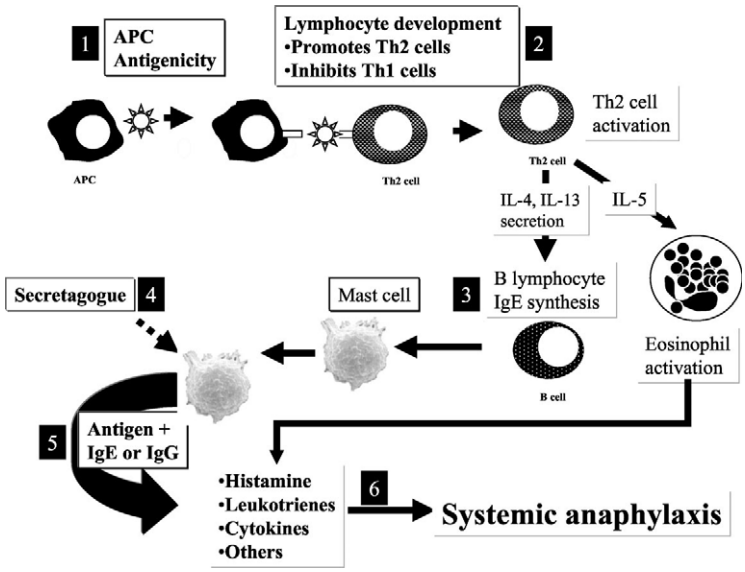

Figure 1. Mechanisms that may be operative in progesterone-sensitive anaphylaxis. (1) Progesterone may act as an antigen, (2) promote type 2 T helper cell development, (3) thereby regulating IgE synthesis and allergy, (4) act as a mast cell secretagogue, or (5) direct mast cell or basophil degranulation in conjunction with specific antibodies (either IgE or IgG). This leads to (6) histamine release, leukotriene production, and cytokine secretion culminating in the manifestations of systemic anaphylaxis.

with no history of spontaneous abortions, and a delivery of a healthy baby occurred.

Paradoxically, but like other allergic diseases,[42] there are many patients whose symptoms improve at exactly the time in pregnancy when levels of progesterone are the highest.[6,10,24–26,34,41] Some suggest the possibility that desensitization occurs through the natural and slow rise of hormone levels in this state,[42] but more likely during pregnancy the increased production of anti-inflammatory glucocorticoids from a hyperfunctioning adrenal pituitary axis causes the improvement.[24] Although there are definite patterns of symptoms of APD during pregnancy, these manifestations also vary and support the idea that there may be multiple mechanisms causing the disorder.

Proof of Antibodies

The proof of the presence of antibodies was initiated by the use of the basophil degranulation test by Shelley et al[20] in his APD patient when he showed degranulation and disappearance of basophils during a clinical flare and in vitro to norethindrone. Next, Farah and Shbaklu[24] used direct and indirect immunofluorescence studies to demonstrate antibodies have a contributory role. Interestingly, in their experiment, the ovary showed fluorescence with the addition of the patient's serum alone, but when free progesterone was added before the addition of the patient's serum the effect was blocked.

Purification of different IgG antibodies has been achieved: an IgG to 17-OHP with a somewhat lesser affinity to progesterone[52] was demonstrated; another test proved an antiprogesterone IgG to both subtypes 1 and 4[29]; and finally an IgG to 17-OHP alone was found.[13] Most cases which demonstrate antibodies, presented with urticaria and angioedema, and at least three cases had demonstrable antibodies using immunofluorescence studies.[24,28,29]

Direct Anaphylactoid Histamine Release?

The possibility that progesterone has direct histamine releasing effects on mast cells and basophils exist, especially in patients manifesting with systemic anaphylaxis in whom no antibodies could be demonstrated. Some studies are limited by the fact that immunofluorescent purification has not been done on progesterone-induced anaphylaxis patients. The only results we have are on eight patients with recurrent idiopathic anaphylaxis (only three of which had positive medroxyprogesterone challenges and all had negative progesterone skin tests) with 10 controls. The investigators were unable to demonstrate direct histamine release from basophils with progesterone or estrogen in the patients or controls. They postulated the possibility that these hormones might actually modulate mast cells (either directly or IgE-mediated) instead of basophils, or that they might increase the responsiveness of mast cells to other degranulation agents.[37] It would be worthwhile to pursue testing of tissue-derived mast cells in patients with progesterone-induced anaphylaxis patients to resolve this issue. This testing may provide credence to a possible mechanism involving the combination of IgG antibodies to progesterone leading to immune complex formation which could act via Fcϵ receptors to trigger mediator release from mast cells.[54]

DIAGNOSIS

Different testing with the hormonal preparation provides the clearest evidence of hormone sensitivity. There is a theoretical risk of precipitating a severe anaphylactic event, and hence must be carried out with extreme caution and by experienced physicians. Skin testing with aqueous progesterone is the first step. Provocative testing is a little more complicated. Intramuscular aqueous progesterone is preferable to DP. DP is a long-acting preparation which contains medroxyprogesterone acetate, but also includes vehicle con-

tents of polyethylene glycol polysorbate, methylparaben, propylparaben, sodium chloride, and water. The vehicle, itself could be a source for a cutaneous or anaphylactic reaction. In fact, there have been at least two reported cases[36,50] of isolated anaphylaxis to DP not previously associated with either APD or recurrent anaphylaxis (Table 2, items 10 and 11). One product when sent for testing failed the foreign protein test as well as created mild anaphylactoid reactions in mice and guinea pigs.[50] Given the longer-acting preparation of DP with the potential for continued reactions after injection, and the possibility of a reaction to the vehicle, we recommend that an aqueous intramuscular progesterone be used for challenging patients with possible progesterone sensitivity instead of DP. A positive test is found when the progesterone creates a skin or systemic reaction upon its injection to the skin. Once the cause is determined, Stephens et al[55] felt that no further work-up is justified in patients who are controlled with anovulatory agents. An algorithm for the evaluation of progesterone-sensitive anaphylaxis is provided in Figure 2.

Wilkinson and Beck[33] recommended an optimum protocol to be used only in patients with severe disease considering oophorectomy. They suggested treating the patient with an LH-RH agonist over 6 months with documentation of clearance of the eruptions/anaphylaxis and hormonal confirmation of absence of ovulation. Then they would recommend a progesterone challenge for specific confirmation. If a flare occurs during testing, the diagnosis is confirmed.[33]

TREATMENT

Evidence shows that various possible treatments exist for the different types of progesterone sensitivity. Because of the differences in symptomatology, separate courses of treatment are advised depending on the manifestation of progesterone sensitivity. It should be noted that sometimes in both APD and anaphylactic reactions, the patient's conditions could resolve/remit spontaneously.

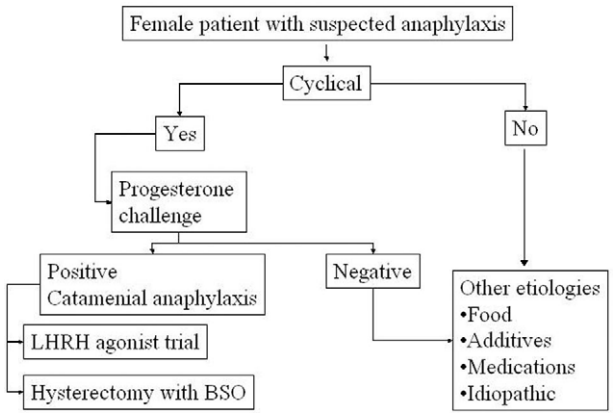

Figure 2. Algorithm for evaluation of a patient with suspected progesterone-induced anaphylaxis.

APD Treatment

If control of a simple APD cutaneous reaction is desired, little to no relief may be found with antihistamines; however, the use of systemic glucocorticoids[27] may be helpful during exacerbations. Side effects of long-term use and the variable control make glucocorticoids a less desirable option.

Early on, desensitization using progesterone was used as a method of control with remission in most, but some patients suffered recurrence of disease within 1 or 2 years after injections were discontinued. This method of treatment has fallen out of favor in the past 10 years. In the past, conjugated estrogens (Premarin, Wyeth Ayerst)[5,9,14,17–20,23–25,28,30] may have been the simplest solution, with most patients improving when treated with high doses until its potential for malignant transformation in endometrial tissue without the balancing effects of progesterone became known.

The 17-α-alkylated steroids such as danazol (Danocrine, Sanofi Winthrop, New York, NY)[15,52,45] or the later generation stanozolol (Winstrol, Sanofi Winthrop)[27] has been used to suppress ovulation in simple dermatologic cases. Some patients responded with an apparent synergistic effect when used with chronic lower doses of glucocorticoid therapy. This therapy can be complicated by elevations of liver function tests and/or hepatic injury.[27] Others felt it was possible in severe resistant cases of APD to treat prophylactically with danazol before the expected onset of menses and continue it 3 days after menses ends. In this way there is no interference with the menstrual cycle itself, and simultaneously the adverse effects seen with long-term treatment with danazol are avoided.[15] It should be noted that danazol therapy was not always successful.[32] One study[13] showed improvement in symptoms with thalidomide realizing that this is a toxic drug with very undesirable side effects. Another drug which has been used is tamoxifen (Nolvadex, Zeneca Pharmaceuticals, Wilmington, DE),[5,6,16,17] which has induced remission of APD.[6] Side effects can include amenorrhea and negative effects on bone metabolism.

Various gonadotropin-releasing hormone (GnRH)/LH-RH agonists have also been proposed for use.[17,21,32,38] One study[32] showed the GnRH agonist buserelin (an investigational intranasal spray), can be used to bring about remission of symptoms, with the main side effect being amenorrhea. In one case,[17] the LH-RH agonist triptorelin (also an investigational agent) was used once a month parenterally, but treatment was discontinued after the second dose caused an episode of hypotension needing treatment with epinephrine and corticosteroids. This reaction is actually typical, as the initial doses of an LH-RH agonist will first stimulate the ovaries and most likely cause an exacerbation of symptoms before its long-term effects of ovarian suppression sets in. The negative effects of GnRH therapy are its expense, and the fact that estrogen supplementation is often needed to avoid menopausal symptoms of hot flashes, vaginal dryness, loss of libido, and loss of bone mineralization.[17] For more severe or refractory cases, Shelley et al[20] in 1964 published the first case where surgical castration with a total abdominal hyster-

ectomy and bilateral oophorectomies was shown to be the definitive treatment. Since that time numerous cases have been successfully treated in the same fashion.[17,19,20,31,35,45,56] Usually this treatment is reserved for patients with refractory and severe symptoms.

Progesterone Anaphylaxis Treatment

Symptomatic therapy must be provided to all patients while definitive diagnosis and specific therapeutic strategies are being developed. Acute anaphylactic reactions associated with the menstrual cycle can be treated symptomatically with antagonists of the histamine H_1- and H_2-receptors, with short courses of glucocorticoids, and/or bronchodilators given during acute flares of airway obstruction or laryngeal edema. One should realize that these interventions may not be uniformly effective or successful and this stresses the need for rapid and efficient evaluation of these patients. Epinephrine autoinjectors (Epipen, Day Pharmaceuticals, Napa, CA) should be provided to all patients who suffer from laryngeal edema, oral or tongue swelling, and/or systemic anaphylaxis.[57–60] This will provide some immediate benefit and may protect the patients with fatal airway obstruction while medical assistance is being sought. Oral contraceptives have led to anaphylactic reactions in some patients and should be discontinued.[21]

Anovulatory medications such as LH-RH agonists mentioned are proven to work in some patients with positive progesterone challenges.[38] In any case, a trial of LH-RH agonist therapy will help convince the physician and the patient that progesterone is playing a major role. This process may assist in decision-making regarding the role of more radical steps such as hysterectomy and oophorectomy (algorithm, Fig 2). If the anovulatory does not work and there are negative hormonal challenges and skin tests, it is still a rare possibility that the patient is reacting to a substance produced by menses such as prostaglandins. A trial of nonsteroidals such as indomethacin (Indocin, Merck, Sharp & Dohme, West Point, PA) in such cases may be worthwhile.[48] Again, with the lack of good controlled trials, a firm recommendation on the use of nonsteroidal agents would be difficult.

The definitive treatment still appears to be oophorectomy[38,48] as described with our own patient. Slater et al[38] depicted one exception in case 2 of their study whose anaphylactoid symptoms improved after bilateral salpingo-oophorectomies with her attacks dropping from 17 to 35 attacks per week to 4 to 7 per week. However, she still required antihistamines to control flushing and bloating. Total hysterectomy with bilateral oophorectomies is still considered the definitive therapy and for most patients with anaphylaxis, the preferred course of treatment, although other options are clearly available (Table 5)

Table 5. Treatment Options for Anaphylaxis Manifestations

Acute symptomatic therapy
Histamine receptor (H_1 and H_2) antagonists
Glucocorticosteroids
Epinephrine
Bronchodilators for bronchospasm
Specific hormone-directed therapy
Conjugated estrogens
Danazol or stanozolol
GnRH/LH-RH agonists-leuprolide acetate
Tamoxifen
Definitive treatment
Total hysterectomy with bilateral salpingo-oophorectomy

CATAMENIAL ANAPHYLAXIS

Catamenial anaphylaxis deserves brief mention because it varies slightly from APD anaphylaxis. Catamenial anaphylaxis differs from APD primarily by the timing of symptoms, which seem to be directly associated with the start of the menstrual flow instead of beginning a few days earlier in the premenstrual phase as in APD. Catamenial anaphylaxis symptoms continue throughout the menstrual flow, instead of ceasing soon after flow begins as in APD, with symptoms ending when menses flow stops. It is thought that in the case of catamenial anaphylaxis, endometrial-derived mediators such as prostaglandin $F_2\alpha$ may leak into the blood stream instead of progesterone causing these reactions, as skin and intramuscular hormone tests are usually negative. One patient was treated successfully with indomethacin (Indocin, Merck Sharpe & Dohme) for 1 month. However, the therapy was discontinued when the patient elected to have a hysterectomy with bilateral salpingo-oophorectomy the next month with resolution of symptoms.[47,48]

CONCLUSION

Patients with APD may present with several different unusual manifestations, resulting in delayed diagnosis. We have focused on the autoimmune dermatologic disorders, which range from a monthly eruption associated with the premenstrual or luteal phase of the menstrual cycle to a continuous cutaneous reaction all the way to recurrent systemic anaphylactic reactions. APD and progesterone-induced anaphylaxis are rare disorders, with only a handful of documented cases, and only one previous review.[49] These disorders primarily affect women as a reaction to progesterone in their luteal phase of their menstrual cycle. The pathogenesis of progesterone-sensitive syndromes, although poorly understood, is slowly being elucidated. However, more studies are required. Management includes a variety of options with the goal of ovulatory suppression with tamoxifen (Nolvadex, Zeneca Pharmaceuticals) or LH-RH agonists providing specific symptomatic hormone-directed therapy, whereas definite therapy almost always rests with hysterectomy and bilateral salpingo-oophorectomy.

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Requests for reprints should be addressed to:
Guha Krishnaswamy, MD
Department of Medicine
PO Box 70622
East Tennessee State University
Johnson City, TN 37614-0622
E-mail: krishnas@etsu.edu

CME Examination

1–5, Snyder JL, Krishnaswamy G. 2003;90:469-477.

CME Test Questions

1. The timing of APD/progesterone anaphylaxis occurring during the menstrual cycle is true in the following EXCEPT:
   a. It is regularly associated with starting at the time of menses and ending with the stop of menstrual flow.
   b. It can start during the premenstrual cycle, usually 2 to 3 days before menstrual flow and decreasing 2 to 3 days after the start of menses.
   c. It can occur at any random time during the menstrual cycle.
   d. It can recur more than once during the menstrual cycle.
2. Which of the following treatments is the most definitive treatment for APD with anaphylaxis?
   a. Tamoxifen.
   b. Conjugated estrogens.
   c. Total abdominal hysterectomy with bilateral salpingo-oophorectomy.
   d. LH-RH agonists.
3. Which diagnostic tests of APD with anaphylaxis help to confirm the diagnosis clinically?
   a. Obtain an antibody screen for 17-OHP IgG.
   b. Do a medroxyprogesterone intramuscular challenge in the office.
   c. Get a direct and indirect immunofluorescent screen.
   d. Obtain a basophil degranulation test.
4. Which statement is false?
   a. Some APD patients' symptoms clear during pregnancy.
   b. Some APD patients' symptoms are worsened during pregnancy.
   c. Some patients with APD also have an association with spontaneous abortions.
   d. Exposure to exogenous progesterone occurs in all patients and causes the initial sensitization of APD patients.
5. Which of the following statements are true?
   a. It is safe for a patient to take progesterone contraceptives if she is experiencing APD symptoms.
   b. H_1- and H_2-blockers are effective treatment modalities to prevent APD symptoms from recurring.
   c. The 17-α-alkylated steroids such as stanozolol and danazol are possible but not ideal treatments for APD without anaphylaxis.
   d. Catamenial anaphylaxis is a progesterone-mediated allergic reaction.

Answers found on page 571.